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Insulinemic and antioxidant status in normoglycemic subjects with parental history of type 2 diabetes mellitus

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Abstract: **Diabetes mellitus is affecting human health all over the world. Both environmental and genetic factors are implicated in its pathogenesis. However, the primary of the factors are still debated. Biochemical mechanism(s) in pancreatic β-cell destructions rendering reduced insulin secretion is postulated to be associated with genetic variation and hence the present proposal was aimed to explore insulin secretory capacity (HOMA-%B), insulin sensitivity (HOMA-%S) and total antioxidant status (TAS) in subjects having parental history of type 2 diabetes mellitus (T2DM) and compared with their negative counterpart.**

In this cross-sectional study, 96 normoglycemic subjects were enrolled, among them 48 subjects (case) had parental history of T2DM, rest 48 without parental history of T2DM (controls). Blood glucose was measured by glucose oxidase method. Serum total cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol were measured using Dimension®RxL max clinical chemistry system, and serum low density lipoprotein cholesterol (LDL) were calculated by Friedewald formula. Serum insulin was measured by enzyme linked immunosorbent assay. HOMA-%B, HOMA-%S and insulin resistance (HOMA IR) were assessed from fasting glucose and insulin using HOMA2 calculator. Total antioxidant status (TAS) was determined by spectrophotometric technique. Data were expressed as median (range) and Mann Whitney U test was performed to calculate statistical difference between groups using GraphPad Prism (6.02). P value < 0.05 was taken as level of significance.

Median (range) of age (years) was 35.0 (30–50) and 36.5 (30–49) in case and controls respectively. Median (range) of fasting and 2hrs plasma glucose (mmol/L) was 4.9 (3.4–7.7) and 5.9 (4.4–10.6) in case and 4.9 (3.5–5.9) and 5.8 (3.8–7.8) in control respectively. Median (range) of fasting serum insulin (µIU/mL) was 16.1 (4.8–53.2) and 13.3 (2.5–46.3) in case and controls which showed statistical difference (p = 0.0134). HOMA-%B was significantly higher in case compared to control [179 (55–381) vs 98 (56–335), p = 0.001]. HOMA %S was significantly lower [49.3 (17.2–95.8) vs 60.2 (15.5–152.9), p = 0.0365] and HOMA IR was significantly higher [2.0 (1.0–5.8) vs 1.7 (0.7–6.5), p = 0.0365] in case compared to control subjects with BMI ≤ 25 Kg/m². No significance difference was observed in TAS between case and control group [1296 (579 – 2164) vs 1549 (737 – 2690) µmol/L, p = 0.1330].

Data concluded that normoglycemic offspring of T2DM subjects had higher insulin secretory capacity as evidenced by absolute circulating insulin level and HOMA-%B as a measure of pancreatic β-cell secretion suggesting possible influence on heightened expression of related genes. The plausible mechanism(s) are yet to be identified. Similar levels of total antioxidant status (TAS) in the two groups preclude the oxidative stress involved in the process.

Keywords: **Antioxidant status, diabetes, insulinaemic, normoglycemic offspring.**

1. INTRODUCTION

Non communicable diseases (NCDs) have emerged as major threat of human health all over the world over the last few decades; type 2 variety of Diabetes Mellitus (DM) in particular, comprises the major component of NCDs[1]. It is estimated that about 415 million people worldwide were affected by DM in 2015 and it is predicted to be 642 million by

2040 [2].In Bangladesh, 7.1 million people were estimated to be affected by DM in 2015 which is predicted to be 13.6 million by the year 2040 [2]. Type 2 diabetes mellitus (T2DM) accounts for about 90% of DM in the world. There are, however, marked variation in its prevalence in different ethnic populations. Among Europeans it varies about 10% [3]. Among Indian Asian the prevalence found to be varied as well. Population based study is lacking in Bangladesh. However, taking inconsideration of small scale studies, prevalence of T2DM assumed to be 7% [4].

The basic pathogenesis in the development of DM include pancreatic β-cell damage resulting in insulin deficiency/or resistance to insulin in peripheral tissue. Both genetic and environmental factors have been implicated in the process of pancreatic islets [5]. Damage of pancreatic β-cells is postulated to result from immune or chemical mediated consequences. Role of heredity in the pathogenesis of DM has been implicated on the basis of aggregation of phenotype in families, twin study, association study and linkage study with the introduction of the powerful tools of Genome-wide analysis which has become the much profound approach by the scientific communities. There is strong evidence that heredity plays an important role in the development of type 2 DM (T2DM). Individuals with strong family history of T2DM are found to be at higher risk than individuals with no family history in developing T2DM [6].

Though both insulin resistance and/or insulin deficiency are the key players for development of T2DM, the chain of events and their relationship in development of T2DM are complex and it is difficult to determine the initial event once the disease is already established [7]. To understand the interaction between heredity and progression to DM, more studies on normoglycemic subjects with family history of DM still importantly required, particularly in Bangladeshi population. Insulin resistance is found to be higher in normoglycemic subjects with strong family history of T2DM [8,9, 10, 11], suggesting that the primary factor of development of T2DM is impaired insulin action. This insulin resistance was present in the normoglycemic subjects with parental history of T2DM even 1-2 decades before the diagnosis of the disease [12,13,14]and during this period, blood glucose remain normal by compensatory hyperinsulinemia [16]. When beta cell fails to compensate insulin resistance by increased insulin production Impaired Glucose Tolerance (IGT) occurs [15].

According to a current hypothesis, oxidative stress plays an important role in beta cell dysfunction, impaired glucose tolerance and ultimately type 2 DM through production of Reactive oxygen species (ROS) [16]. Oxidative stress results from imbalance between production and utilization of ROS through stimulation of polyol pathway, formation of advanced glycation end product (AGE), activation of protein kinase C (PKC) [16,17]. In DM, hyperglycemia induces over production of ROS due to imbalance between redox status [3]. Oxidative stress induced tissue damage in particular to pancreatic β-cell damage is claimed to be associated with both type 2 and type 1 DM.

2. METHODOLOGY

The study subjects were recruited purposively from the department of Applied Laboratory Sciences, Bangladesh University of Health Sciences (BUHS), Dhaka, Bangladesh. 96 Bangladeshi adult subjects were included in this study. Among them 48 nondiabetic subjects had parental history of T2DM, 48 were age-sex matched healthy nondiabetic controls without parental history of T2DM. Written consent was obtained from willing subjects. Subjects with serious comorbid diseases were excluded. From the out-patient department of BIHS general hospital attending for the diagnosis of diabetes mellitus, subjects with or without parental history of T2DM (according to WHO criteria, IDF 2012) were recruited. Standing height was measured using appropriate scales without shoesnto the nearest millimeter. Weights of all individuals were measured wearing light clothing without shoes and hats in nearest 0.5 kg. Body mass index (BMI) of the subjects were calculated using standard formula (BMI = Weight (Kg)/[Height (m)]^2). Blood pressure was measured to the nearest 1 mm Hg with mercury sphygmomanometers using standard recommended procedures. Blood pressure was measured to the nearest 1 mm Hg with mercury sphygmomanometers using standard recommended procedures.

After eight to ten hours of fasting blood was collected between 8.00-9.00 am using correct venipuncture technique. Subjects were given 75g of glucose in 250-300 ml of water. After 2 hours second blood sample were collected. Fasting & 2 hours plasma glucose concentration was determined by spectrophotometric technique using glucose-oxidase method. Serum total cholesterol(TC), serum triglycerides (TG), serum high density lipoprotein (HDL)is measured using Dimension® clinical chemistry system (Siemens Healthcare Diagnostics Inc. USA).The LDL-Cholesterol concentrations in serum were calculated by Friedewald's formula (Friedewald et al, 1972). Serum insulin was measured by a solid phase enzyme-linked immunosorbent assay (ELISA) using DRG Insulin ELISA Kit. Insulin secretory capacity i.e., β-cell function (HOMA B), insulin sensitivity (HOMA S) and insulin resistance (HOMA IR) were calculated from fasting plasma glucose (mmol/L) and fasting serum insulin (μIU/ml) using HOMA2 calculator version 2.2.3 available online (provided by the Diabetes Trials Unit, University of Oxford). Total antioxidant capacity (TAC) was determined by spectrophotometric technique according to Benzie and Strain (1996).

Statistical Methods

The results were presented as median and range. Significance was assessed at 5 % level of significance. Mann-Whitney U test was performed to find the significance of statistical test using GraphPad Prism version 6.04 for Windows.

3. RESULTS

Characteristics of the study subjects:

Characteristics of the study subjects were presented in Table 1. Both groups were matched for age, sex and BMI (p >0.05) (Table 1). No significant difference was observed in degree of hypertension and glycemic status between normoglycemic first degree relatives with parental history of T2DM and without parental history of T2DM (Table 1). Among the lipid parameters studied, total cholesterol and low-density lipoprotein cholesterol were significantly higher in subjects with parental history of T2DM compared to control (Table 1).

Table 1: Characteristics of the study subjects

Variables	Case	Control	p value
Age (Years)	35.0 (30 - 50)	36.5 (30 - 49)	0.3301
Gender (Male/Female)	23/25	28/20	0.4135
Body mass index (Kg/m^2)	25.9 (18.5 - 35.5)	25.0 (18.8 - 33.3)	0.0884
Blood pressure (mmHg) Systolic Diastolic	 110 (80 - 140) 80 (60 -100)	 110 (90 - 130) 70 (60 -100)	 0.6603 0.5431
Fasting plasma glucose (mmol/L)	4.9 (3.4 - 7.7)	4.9 (3.5 - 5.9)	0.9198
2 hour plasma glucose (mmol/L)	5.9 (4.4 - 10.6)	5.8 (3.8 - 7.8)	0.1485
Total cholesterol (mg/dL)	173 (100 - 289)	157 (84 - 301)	0.0107
HDL cholesterol (mg/dL)	32.5 (21 - 51)	35 (23 - 59)	0.0957
LDL cholesterol (mg/dL)	106.6 (34.8 - 248.4)	89.4 (44 - 203.2)	0.0311
Triacylglycerol (mg/dL)	129.5 (65 - 479)	148 (57 - 363)	0.2862

Case, Subjects with parental history of T2DM; Control, Subjects with parental history of T2DM; Results were expressed as median (range). Mann-whitney test was performed to calculate statistical difference between the groups.

Table 2: Comparison of insulinemic and antioxidant status between subjects with or without parental history of diabetes mellitus

Variables	Case	Control	p value
Fasting insulin	16.1(4.8-53.2)	13.3(2.5-46.3)	0.0134
BMI ≤25	14.5(7.1-53.2)	11.0(4.3-46.3)	0.0083
BMI >25	16.9(4.8-48.9)	13.8(2.5-31.7)	0.3040
HOMA %B	179(55-381)	98(56-335)	<0.001
≤25	179(92-328)	98(57-335)	0.0006
>25	179(55-381)	97(59-284)	0.0029
HOMA %S	43(15-132)	51(16-282)	0.0617
≤25	49.3(17.2-95.8)	60.2(15.5-152.9)	0.0365
>25	40.5(14.6-131.7)	46.7(22.4-281.6)	0.4741
HOMA IR	2.3(0.8-6.8)	2.0(0.4-6.5)	0.0617
≤25	2.0(1.0-5.8)	1.7(0.7-6.5)	0.0365
>25	2.5(0.8-6.9)	2.1(0.4-4.5)	0.4741
TAS (µmol/L) BMI ≤ 25 kg/m^2 BMI > 25 kg/m^2	1296(579-2164) 1210 (570 - 2164) 1334 (743 - 2163)	1549(737-2690) 1489 (737 - 2690) 1590 (868 - 1839)	0.1330 0.0583 0.5961

Case, Subjects with parental history of T2DM; Control, Subjects with parental history of T2DM; Results were expressed as median (range). Mann-whitney test was performed to calculate statistical difference between the groups.

Table 2 shows the median (range) of insulinemic and antioxidant status in subjects with or without parental history of type 2 diabets mellitus. Medians of fasting insulin in case and control were 16.1 (4.8 - 53.2) µmol/I and 13.3 (2.5 - 46.3) µmol/I respectively and it was significantly higher in case compared to control ($p = 0.0134$). Median of HOMA %B was also significantly higher in case compared to control (179 (55 - 381) vs 98 (56 - 335), $p < 0.001$) (Table 2). When analyzed according to BMI, fasting insulin showed significant difference only between subjects with and without parental history of T2DM among lean (BMI $\leq$ 25 kg/m^2) whereas, HOMA %B differed significantly among two BMI groups (Table 2).

Insulin sensitivity as assessed by HOMA-%S was 43 (15 - 132) and 51 (16 - 282) in case and control respectively and it was lower in case compared to control. Insulin resistance as assessed by HOMA IR was 2.3 (0.8 - 6.8) and 2.0 (0.4 - 6.5) in case and control respectively which did not show statistical significant difference (Table 2). When analyzed according to BMI groups, both HOMA %S and HOMA IR differed significantly between subjects with and without parental history of T2DM among subjects with BMI $\leq$ 25 kg/m^2 (Table 2).

The medians (range) of total antioxidant status were 1296 (579 - 2164) µmol/L and 1549 (737 - 2690) µmol/L in case and control respectively which did not show statistical significant difference between case and control irrespective or respective of BMI groups (Table 2).

4. DISCUSSION

Impaired β-cell function and/or insulin resistance attributed to the primary underlying mechanism of T2DM but a considerable variation exists in insulin secretion and insulin resistance regarding race, lifestyle and nutritional factors. Heredity plays an important role in the development of diabetes mellitus with complex interaction with environmental factors. In this study, we aimed to determine insulinemic and antioxidant status in subjects with parental history of diabetes mellitus in reference to normoglycemic controls without parental history of T2DM.

Various methods had been used to measure insulinemic status, among them Euglycemic insulin clamp test is considered as the gold standard method. However, due to infeasibility, various studies [18, 19, 20] have considered Homeostasis Model Assessment method as standard method for measuring insulinemic status in clinical practice and population based research.

In this study, fasting insulin concentration was significantly higher in subjects with parental type 2 diabetes mellitus compared to control representing insulin hyper secretion as assessed by HOMA%B. This finding is consistent with the study of Strączkowski et al [21] on lean adults of Polish people.

My study showed decreased insulin sensitivity (HOMA %S) in subjects with parental history of T2DM compared to controls but it was not statistically significant. However, when the groups were divided according to BMI, subjects with parental history of T2DM whose BMI are ≤25 showed significantly lower insulin sensitivity then that of control groups with BMI ≤25. This finding is in concordance with the findings of other studies done on subjects with strong family history of T2DM [23] found hyperinsulinemia (40.6±15.8 vs 30.9±13.6 µmol/I $p = 0.005$) in offspring of type 2 DM when compared to control group with no parental history of T2DM. Lower insulin sensitivity and higher insulin resistance were also found in subjects with parental history of type 2 DM.

Our study also showed increased insulin resistance (HOMA IR) in subjects with parental history of T2DM compared to controls but it was not statistically significant. However when the groups were divided according to BMI, subjects with parental history of T2DM whose BMI were ≤25 kg/m^2 showed significantly higher insulin resistance then that of control groups with BMI ≤25 kg/m^2. This finding is in concordance with the findings of Straczkowski et al, 2003[21]. The study involved lean subjects with strong family history of T2DM [21]. They found that offspring of T2DM parents had markedly higher insulin resistance then control group. They concluded that insulin resistance is present even in young, lean subjects at high risk for the development of T2DM.

The reason for difference in insulin sensitivity and insulin resistance between two groups being not significant may be related to the method we used. The gold standard for measuring insulinemic status is hyperinsulinemic clamp technique. Since this method requires a considerable experience and extensive equipment. Homeostasis model assessment (HOMA) is easier method for estimating insulinemic status was used in present study. However, this index has low sensitivity and specificity for detecting insulin resistance in non-diabetic individuals [23].

Oxidative stress was measured by total antioxidant capacity (TAS) and it was found significantly lowered in lean subjects. In the study of Rizvi et al [24] found that erythrocyte plasma membrane redox system (PMRS) and ascorbate free radical (ARF) reductase are increased in first degree normoglycemic relative of type 2 DM subjects. The increase shows a compensatory mechanism to reduce oxidative stress which means that a disturbance in glucose homeostasis in type 2 diabetic families occur due to impaired redox balance even before development of type 2 DM.

5. CONCLUSION

On the basis of the results of this study, it may be concluded that -

i. Normoglycemic offspring of T2DM subjects had higher insulin secretory capacity as evidenced by absolute circulating insulin level and HOMA-%B as a measure of pancreatic β-cell secretion suggesting possible influence on heightened expression of related genes.

ii. Similar levels of total antioxidant status (TAS) in the two groups preclude the oxidative stress involved in the process.

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